

Applicants: Jane H. Morse and James A. Knowles
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Amendments to the claims:

Certain claims have been amended and others canceled below without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in a continuation application.

The following listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims:

1. (amended) A method of detecting whether a subject is predisposed to, or afflicted with, a pulmonary ~~disease~~ hypertension which comprises (1) obtaining a suitable sample containing bone morphogenetic protein receptor II or nucleic acid encoding same from the subject; and (2) detecting in the bone morphogenetic protein receptor II or nucleic acid encoding same ~~sample~~ whether a bone morphogenetic protein receptor-II mutation which is not present which is not present in wildtype bone morphogenetic protein receptor-II or nucleic acid encoding same,

wherein the presence of such a mutation indicates that the subject is predisposed, to or afflicted with, the pulmonary ~~disease~~ hypertension.
2. (amended) The method of claim 1, wherein the suitable sample ~~is~~ comprises ~~a nucleic acid sample, and the~~

~~mutation is detected in~~ a nucleic acid encoding bone morphogenetic protein receptor-II.

3. (amended) The method of claim 1, wherein the suitable sample ~~is one which~~ comprises a bone morphogenetic protein receptor-II polypeptide, ~~and the mutation is detected in the bone morphogenetic protein receptor-II polypeptide.~~

4. (amended) The method of claim 1, wherein the pulmonary ~~disease~~ hypertension is Primary Pulmonary Hypertension.

5. (original) The method of claim 4, wherein the Primary Pulmonary Hypertension is Familial Primary Pulmonary Hypertension.

6-50. (canceled)

51. (amended) A method of predicting an increased likelihood of a subject giving birth to twins or triplets which comprises:

- a) obtaining a suitable nucleic acid sample from the subject;
- b) detecting the presence of one copy of a ~~mutant~~ nucleic acid which encodes a mutant bone morphogenetic protein receptor-II ~~polypeptide~~, thereby indicating that the subject is heterozygous

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for the ~~mutation~~ mutant bone morphogenetic protein
receptor II,

wherein heterozygosity predicts an increased likelihood
of the subject giving birth to twins or triplets.

52. (amended) A method of predicting an increased likelihood
of a pregnant subject having a miscarriage ~~prior to
giving birth to a child~~ which comprises:

- a) obtaining a suitable nucleic acid sample from the
subject;
- b) detecting the presence of two copies of a ~~mutant~~
nucleic acid, each of which encodes a mutant bone
morphogenetic protein receptor-II ~~polypeptide~~,
thereby indicating that the subject is homozygous
for the ~~mutation~~ mutant bone morphogenetic protein
receptor II,

wherein homozygosity predicts an increased likelihood of
the subject having a miscarriage ~~prior to giving birth
to a child~~.

53. (withdrawn)

54. (canceled)

55. (withdrawn)

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56. (amended) A method of detecting whether a subject is either predisposed to, or afflicted with, Familial Primary Pulmonary Hypertension which comprises:

- a) obtaining a suitable nucleic acid sample from the subject; and
- b) detecting the presence of a (GGC)₁₂ trinucleotide repeat at positions corresponding to positions -928 to -963 in the 5' end of the subject's bone morphogenetic protein receptor-II gene,

wherein the presence of the trinucleotide repeat indicates that the subject is either predisposed to, or afflicted with, Familial Primary Pulmonary Hypertension.

57. (withdrawn)

58. (canceled)

59-60. (withdrawn)

61-63. (canceled)

64. (new) The method of claim 2, wherein the mutation described relative to a difference from the sequence encoding wildtype bone morphogenetic protein receptor II set forth in SEQ ID NO:1 is selected from the group consisting of:

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- (1) a deletion of nucleotides having the sequence guanosine-guanosine-guanosine-guanosine-adenosine located at positions 1099-1103;
- (2) a deletion of a thymidine nucleotide located at position 2579;
- (3) a substitution of nucleotides having the sequence cytosine-thymidine-thymidine-thymidine located at positions 507-510 with nucleotides having the sequence adenosine-adenosine-adenosine;
- (4) a substitution of a cytosine nucleotide located at position 2617 with a thymidine nucleotide;
- (5) a substitution of nucleotides having the sequence adenosine-guanosine located at positions 690-691 with a thymidine nucleotide;
- (6) a substitution of a cytosine nucleotide located at position 1471 with a thymidine nucleotide;
- (7) a substitution of a guanosine nucleotide located at position 1472 with an adenosine nucleotide;
- (8) a deletion of nucleotides having the sequence adenosine-thymidine-thymidine-thymidine located at positions 1248-1251;
- (9) a substitution of a cytosine nucleotide located at position 994 with a thymidine;
- (10) a substitution of a thymidine nucleotide located at position 295 with a cytosine nucleotide;
- (11) a deletion of a guanosine nucleotide located at position 1097;

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- (12) a substitution of a guanosine nucleotide located at position 727 with a thymidine nucleotide;
- (13) a deletion of an adenosine nucleotide located at position 1214;
- (14) a deletion of nucleotides having the sequence adenosine-cytosine located at positions 2441-2442;
- (15) a substitution of a cytosine nucleotide located at position 2695 with a thymidine nucleotide;
- (16) a deletion of 21 nucleotides located at positions 189-209;
- (17) a substitution of a guanosine nucleotide located at position 296 with an adenosine nucleotide;
- (18) a substitution of a thymidine nucleotide located at position 250 with a cytosine nucleotide;
- (19) a substitution of a guanosine nucleotide located at position 1040 with an adenosine nucleotide.

65. (new) The method of claim 3, wherein the mutation described relative to a difference from the wildtype bone morphogenetic protein receptor II sequence set forth in SEQ ID NO:2 is selected from the group consisting of:

- (1) a mutation at a glutamic acid residue located at position 368 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;
- (2) a mutation at an asparagine residue located at position 861 which causes the protein sequence thereon to

be different from the wildtype bone morphogenetic protein receptor II sequence;

(3) a substitution of a cysteine residue located at position 169 which causes premature termination of the protein sequence;

(4) a substitution of an arginine residue located at position 873 which causes premature termination of the protein sequence;

(5) a mutation at a lysine residue located at position 230 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;

(6) a substitution of an arginine residue located at position 491 with a tryptophan residue;

(7) a substitution of an arginine residue located at position 491 with a glutamine residue;

(8) a substitution of a phenylalanine residue located at position 417 which causes premature termination of the protein sequence;

(9) a substitution of an arginine residue located at position 332 which causes premature termination of the protein sequence;

(10) a substitution of a cysteine residue located at position 99 with an arginine residue;

(11) a mutation at a proline residue located at position 366 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;

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(12) a substitution of a glutamic acid residue located at position 243 which causes premature termination of the protein sequence;

(13) a mutation at an aspartic acid residue located at position 405 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;

(14) a mutation at a histidine residue located at position 814 which causes the protein sequence thereon to be different from the wildtype bone morphogenetic protein receptor II sequence;

(15) a substitution of an arginine residue located at position 899 which causes premature termination of the protein sequence;

(16) a deletion of consecutive amino acids having the sequence serine-threonine-cysteine-tyrosine-glycine-leucine-tryptophan located at positions 64-70;

(17) a substitution of a cysteine residue located at position 99 with a tyrosine residue;

(18) a substitution of a cysteine residue located at position 84 with an arginine residue;

(19) a substitution of a cysteine residue located at position 347 with a tyrosine residue.